

# History, Progress, and Current Treatment of Parkinson's Disease,

1817 – 2002

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James Parkinson, a British physician, who was born in 1755 and died in 1828, was more known for his unpopular views of social reform than for what he later became famous for. He was anti-war, anti-military, believed in what today would be called socialism, supported civil disobedience, and did as much work with his hobbies, geology and paleontology, as he did with medicine. He was even implicated in a plot to assassinate King George III with a poisoned dart fired from a popgun, but he was later cleared of that charge. He studied Latin and Greek as a young man, and came to medicine by taking over his father's job as a general practitioner in a suburb of London. He wrote a little-known paper on "The Nature and Cure of Gout" in 1805; but this was followed, in 1817 by his classical "Essay on the Shaking Palsy" which attached his name forever to this illness. He was, however, never honored for his astute observations; and there is not even a likeness of Dr. Parkinson available in this time.

Dr. Parkinson, while observing people on the streets of London, noted that some suffered from a tremor which, along with muscle weakness, worsened with time. The Latin name for this condition was "Paralysis agitans", or the "shaking palsy"; but with no standardized neurological examination available at that time, the symptom complex which is well-known today, was not understood in the early Nineteenth century. Despite the lack of a standardized method of diagnosis, however, one of the main features of the detection of this condition was established from the beginning; that of careful observation of the patient.

It was not until the very late portion of the Nineteenth century that physicians began to understand the anatomy and physiology of the nervous system. Pioneering work by such greats in anatomy and physiology as Ramon y Cajal (from Spain) and Sherrington (Britain) began to show us the fine anatomy of the brain; and when studies were made of the brains of those patients who had died with the "Shaking Palsy", now named Parkinson's Disease after the man who first described the external symptoms, it was learned that certain areas of the brain seemed to be affected. These areas, including such structures as the *substantia nigra* (so named because the tissue is black with pigment), *globus pallidus*, parts of the thalamus, were all joined together in a generic description as the "basal ganglia", or collections of nerve cells at the base of the brain. When we talk about the basal ganglia, we are talking about these multiple areas, many of which play a role in other illnesses as well which are different from Parkinson's Disease, but are also associated with similar symptoms.

As knowledge grew and the physiology of the nervous system began to be understood, it became apparent that Parkinson's disease was a disease of both muscle weakness and abnormal movement. The tremor of Parkinson's disease is described as a typical "pill-rolling" tremor, low in frequency (about 4-5 cycles per second); and is a "tremor at rest", meaning that it is most pronounced when the patient is not making a voluntary movement, and it tends to decrease or even disappear with voluntary movement. Years ago, when I first moved to Berkeley, I had a dentist who had early Parkinson's disease and who, when he was talking to me, had a mild tremor. One would think that I might have been concerned at his ability to do dental surgery on me; but I was confident that, once he began to engage in voluntary muscle activity, his hands would become steady; and I remained with that dentist for some years until he retired. And I still have my teeth, too!

Early on, too, it was found that patients with Parkinson's disease, as the illness progressed, developed a slowness of muscle function, and an associated rigidity of the voluntary muscles, which, when the muscles were passively moved through their range of motion, were felt as having "cogwheeling", a grinding sensation to the examiner as the rigidity and the tremor combined. Further, it was noted that the increasing rigidity eventually affected the facial muscles, causing a rather drawn and monotonous facial expression, which has been named the "Parkinsonian mask"; and that the increasing tightness of the lower extremity muscles resulted in a characteristic compulsive gait

where the patient has difficulty starting to walk, but once started, would walk with small steps in a rapid and sometimes increasingly uncontrolled pace, called a “festinating gait”; or as the French called it, “Marche a petit pieds” (“walking with little feet”)

Finally, it was noted that, along with the slowness of movement (“bradykinesia”), came a tendency towards a slowing down of intellectual function, and that this, in time, led to dementia which, in the later stages of the illness, could be quite crippling. Death associated with Parkinson’s disease usually was not as a direct result of the illness, but rather of the decreasing levels of activity of the patient brought on by the disease, and eventual development of pneumonia or other conditions associated with inactivity. Thus, to this day, maintenance of as active life as is possible is one of the ways to prolong life in patients with Parkinson’s disease.

The cause of Parkinson’s disease is still not known. There are certain forms of Parkinson’s disease that have been associated with such things as viral infection of the central nervous system. The 1918 Influenza Pandemic, which killed more people than did the Black Death in Medieval Europe, produced many cases of Parkinson-like disease due to the encephalitis associated with the Influenza virus, and this form of the illness, called “Post-encephalitic Parkinsonism” frequently affects only one side of the body, whereas the traditional form of Parkinson’s disease is usually bilateral.

There are other associations of conditions with a Parkinsonian-like syndrome, including certain toxic exposures such as carbon disulfide, carbon monoxide, and a chemical named MPTP, sometimes used as a “recreational drug”. Additional causes include other degenerative neurological diseases, including Alzheimer’s disease; Huntington’s disease; side-effects from certain psychiatric drugs such as medications in the Thorazine/Haldol family; and acute or chronic head injury problems. A condition called “normal pressure hydrocephalus”, a variant of degenerative brain disease, may also produce Parkinsonian-like symptoms. The management of these “Parkinsonian-type” conditions is, however, different from the management of the typical case of Parkinson’s disease, and I will limit my presentation today to the “traditional” Parkinson’s disease. I will, however, be happy to answer questions concerning the other types at the end of this talk.

The early diagnosis of Parkinson’s disease is difficult and subtle. Frequently, the first sign is that of decreased movement, and there is a great story about two famous British neurologists (with famous names that you will chuckle over) concerning the early diagnosis of Parkinson’s. Sir Henry Head, a pioneer in British neurology, had a habit of shaking his leg while he sat in an auditorium listening to a lecture; and one day, Russell Brain (later given the title of “Lord Brain”), noted that Sir Henry was not shaking his leg anymore. Brain said that he thought that Sir Henry Head was showing the early signs of Parkinson’s disease, and he turned out to be quite correct. In the case of my own father-in-law, also a physician, he came to stay with me while recovering from surgery associated with a bad fall which he had taken at home; and, as I had the chance to observe him constantly, it rapidly became apparent that he had early Parkinson’s disease; and, in fact, that was probably the cause of his fall. After proper medication, he did well for many years before passing away a few years ago at the age of 91.

When Parkinson’s disease is suspected, a good neurological evaluation is mandatory. This is so that the other causes of similar symptoms can be explored, as the treatments for those conditions are often very different than those used for Parkinson’s disease of the “traditional” type. Such an evaluation should include a careful history and neurological examination; imaging studies, beginning with at least, a CT scan of the brain; and, if there is evidence of enlargement of the spinal fluid pathways, followed by a radioisotope study called a “cisternogram” involving injection of a tracer into the spinal fluid and several days of scanning thereafter to look for “normal pressure hydrocephalus”. Although there are physicians who consider themselves “movement disorder specialists”, I believe that a well-trained neurologist or neurosurgeon should be able to complete a proper evaluation of a patient for Parkinson’s disease.

### Treatment

In the years after the disease was described by Parkinson, there was very little that could be done to alleviate the symptoms. It was, however, noted early on, that advanced Parkinson’s disease was characterized by excessive drooling; and so, drugs, called “anticholinergics”, which dry up mouth secretions, were tried as a treatment. Surprisingly, these treatments seemed to help in many cases to reduce the drooling, and also were found to decrease the tremor as well. We now know that this occurred because of the effect of these drugs in blocking the abnormal nerve transmissions which go along with Parkinson’s disease; and anticholinergics, such as Artane® and Cogentin®, are still used early on in Parkinson’s disease, especially in those cases where tremor is a predominant symptom.

The other thing which was noted early in the history of the knowledge of this disease, was that if a patient with Parkinson’s disease had a stroke, the side affected by the stroke would show improvement in, or even disappearance of the Parkinsonian tremor. This led to the next breakthrough in the treatment of Parkinson’s when surgical procedures were tried to interrupt the voluntary motor pathways of the brain in order to alleviate tremor, and,

to a lesser extent rigidity. These procedures, however, offered a “trade-off”; a partial paralysis in return for a decrease in tremor, and were certainly not a definitive answer.

One day, in the early sixties, Dr. Irving Cooper, a New York neurosurgeon, was performing such an operation, when he inadvertently tore a small artery which supplied a portion of the basal ganglia. He aborted the operation because of this; and, to his pleasant surprise, when the patient awoke from the anesthetic, his tremor was gone and he did not have the partial paralysis that the originally-planned operation would have produced. Dr. Cooper then went about studies to determine what had happened, and he discovered that the injury to the artery had caused the death of a small area of tissue within the globus pallidus; and Dr. Cooper then went about experiments where the globus pallidus and other parts of the basal ganglia were attacked. These areas included, in addition to the globus pallidus, portions of the thalamus, putamen, subthalamus, and others; and the means of producing the lesions have varied from chemicals (alcohol was used by Dr. Cooper), to radioactive implants (we used a strontium-90 needle at the University of Chicago where I trained in the sixties), to freezing, to heating with radiofrequency current; but the main object was the same, to interrupt what was felt to be an “abnormal circuit” between parts of the basal ganglia.

In the mid-sixties, Dr. Nicholas Cotzias and his associates discovered the relationship between the natural neurotransmitter Dopamine and the cause of Parkinson’s disease; and his group devised a way to get a precursor of Dopamine into the brain by synthesizing the chemical L-DOPA. The results of this new treatment were dramatic; and this was followed by almost overnight abandonment of the surgical procedures which had been developed in the early sixties, which, although they were effective, did not seem to be permanent, and many of the patients who were initially improved after surgery on the basal ganglia relapsed after several years.

Sadly, however, it was subsequently determined that the use of L-DOPA, while dramatic initially, was limited by a problem of growing tolerance to the beneficial effects of the medicine, this resulting in the need to increase the dose over time, and eventually making the side-effects worse than the beneficial effects. Thus, excessive dosage with L-DOPA or its relatives could lead to worsening of the abnormal movements (“dyskinesias”), gastrointestinal symptoms, insomnia, hallucinations, and even psychosis, while the beneficial effects would decrease with time.

Some agents, called “neuroprotective agents” were likewise developed, the most common being Selegiline (Deprenyl® or Eldepryl®), which have been added to anti-Parkinson regimens to try and delay the need for use of high doses of L-DOPA; but the results of the use of such drugs, while seemingly beneficial early on, are not totally clear.

Because of the problems associated with L-DOPA, in the eighties and nineties, the surgical approach was once again investigated. Dr. Lauri Laitinen, a neurosurgeon working in Sweden, refined some of the old basal ganglion procedures, and developed a somewhat more precise and elegant method of placing destructive lesions in the globus pallidus and elsewhere. When the globus pallidus was lesioned, the procedure was called “pallidotomy”; and some investigators found that pallidotomy had some benefit in reducing the amount of L-DOPA needed to control the symptoms, as well as the fact that it seemed to improve the physical “slowness” associated with the rigidity. Pallidotomy, however, did not seem to help the dementia very much, and, as the procedural indications were developed, demented patients were usually excluded from those who were offered pallidotomy. Lesions placed in the thalamus, called thalamotomy, seemed to have positive effects on tremor, but did little for rigidity or “slowness”. There was a strong flurry of basal ganglion surgery in the nineties with many centers and even privately-practicing neurosurgeons offering pallidotomy, but, as was predicted by others, the results have not lived up to hopes for these procedures, and they, essentially destructive operations, are once again losing favor.

During the last few years, some new and exciting progress has been made in the treatment of Parkinson’s disease. It has been discovered that, rather than destroying basal ganglion tissue, one could *stimulate* certain areas of the brain and virtually instantly block the abnormal movements and other features of Parkinson’s disease. The area of the brain which seems to be most productive for this type of stimulation is the *subthalamic nucleus (STN)*, located just under the main thalamic area, and placement of implanted electrodes into the subthalamic nucleus followed by stimulation of this area with a pacemaker-like device has been shown to be the most effective surgical treatment to date of this disease. Placement of such devices (called *deep brain stimulators or DBS*), while tedious and not without risk, is rapidly becoming the “gold standard” of treatment for those with Parkinson’s disease who are no longer benefited by treatment with drugs. As with the initial enthusiasm for pallidotomy, one should be cautious with regard to DBS; but, for a number of reasons, this approach seems to be very positive these days.

On the horizon, hopefully, is research which will help to determine the true cause of Parkinson’s disease. It is known that the pathological process involves death of Dopamine-producing cells in the substantia nigra of the midbrain, and much of the current research is devoted to methods which either prevent this cell death; or, which develop a process to “re-charge” this area of the brain with new cells that will once again produce Dopamine.

Thus the use of embryonic cells, called *Stem Cells* has been proposed as a way to try and inject sources of Dopamine into the brains of people with Parkinson's disease. In the past, certain surgeons of somewhat questionable background have attempted to use such cells from other animals such as pigs or monkeys; but use of cells from other species has been clearly shown to be ineffective, and possibly quite dangerous. The use of human embryonic cells has led to some controversy as to the morality of such; but thusfar, the implantation of such cells has not been shown to be significantly helpful. A recent study, done in New York and Colorado, has shown that, while one can get the cells to "take" (and survive), the problems of excessive movements and dyskinesias have overshadowed the benefits of the procedure, and that much more research needs to be done before the use of stem cells can be justified as a mainstream treatment for Parkinson's disease.

I had originally planned to include a discussion of the "standard" treatment for Parkinson's disease in 2002. With the limited time, however, I am not going to spend a great deal of time on that subject except to give you a brief outline for the clinical diagnosis and treatment of this disease. *All* cases of suspected Parkinson's disease deserve the evaluation and workup which I mentioned earlier, including appropriate imaging studies. Once the diagnosis is confirmed, one generally divides the patients into two groups, "early onset" and "late onset", with the age of 60 being the "dividing line". The treatment is somewhat different for the two groups, as the "early onset" patients are going to require a longer period of treatment than are the "late onset" patients.

In the early-onset patients, especially those in which the predominant symptom is tremor, the use of the anticholinergic drugs such as Artane® and/or Cogentin® is generally considered first. Addition of adjuvant drugs such as Amantidine (Symmetrel®) may help with all features of the disease and have low side-effect problems. As the disease advances, L-DOPA is added. Selegiline may have a mild "neuroprotective effect", but this is not clear.

In the late-onset patients, the tendency is to proceed to L-DOPA earlier on, especially where rigidity and/or "slowness" are the most prominent symptoms; and, once again, the use of Selegiline is not settled.

If/when the situation with the L-DOPA treatment reaches the point where the side-effects are becoming intolerable, other approaches can be considered. A new class of drugs, called "Dopamine agonists" have recently been developed which seem to be nearly as effective as L-DOPA itself, but these drugs have a different set of side-effects, some of which, like the "sleep attacks" associated with the drugs Pramipexole (Mirapex®) and Ropinirole (Requip®), can be as dangerous as those seen with L-DOPA. Likewise, the Dopamine agonists are much more expensive than are the L-DOPA medications. Another drug, Cabergoline (Pergolide®) is being tried, mainly outside of the United States, as a substitute for L-DOPA, but the results with Pergolide are not totally clear, either.

To me, if a patient with Parkinson's disease reaches a point where the drug therapy is either no longer effective, or the side-effects are unacceptable, I will refer the patient for a surgical approach. If the problem is purely one of tremor (and this is very rare in a late-stage patient), I would consider thalamotomy. In all other instances, the procedure of choice would be deep brain stimulation. In my opinion, pallidotomy has, once again, dropped far down the list of possible treatments for this illness.

For those of you who are Internet users, I would like to recommend a Mailing List for people with Parkinson's disease. This List is made up of a group of patients, their families, and some medical professionals (doctors, nurses, social workers, etc.) who share an interest in this disease. I find myself learning something virtually every day from reading this List. It is available both as a standard List (you get a message every time someone posts one), or in Digest form (you get one big message at the end of each day, containing all of the postings from that day). To join, send a message to:

[listserv@listserv.utoronto.ca](mailto:listserv@listserv.utoronto.ca)

and, with no subject line, send the following message (exactly):

subscribe parkinsn youremailaddress

with "parkinsn" spelled exactly and "youremailaddress" being your own address (without the quotation marks). When you are enrolled, you will get a message containing instructions for using the List, and also directions as to how to sign off should you decide to leave the List in the future. See you on the List!

(On the table/in the back of the room) are some materials on this subject. I will also place there a transcript of this talk, as well as some material from a man named Bill Harshaw, from the Parkinson List. Bill is a 21-year

veteran of Parkinson's disease, and had implantation of his deep brain stimulator in 1994 in Canada. It continues to give him excellent relief from his symptoms.

Bill has written a booklet entitled, "Neurosurgery For Parkinson's Disease: A Patient's Perspective", and he has donated some copies of this booklet for this talk. Please feel free to take a copy. Bill is also the author of a softcover book entitled, "My Second Life: Living with Parkinson's Disease" and this book is available for \$15.00 (US) plus \$5.00 for postage. Please order your own copy from:

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CANADA

Now, I will be pleased to take your questions.

END

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